APPENDIX "A"

Copy of a "Declaration of Stephen P. Arneric Pursuant to 37 C.F.R. § 1.132" filed in and during prosecution of the grandparent application (U.S. Serial No. 09/599,213, now U.S. Patent No. 6,465,458).

PATENT

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants: Erik H.F. Wong et al.	)
Serial No.: 09/599,213	)
Filed: June 22, 2000	)
Title: METHOD OF TREATING OR PREVENTING CHRONIC PAIN WITH A HIGHLY SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITOR (*As Amended*)	)
Group Art Unit: 1614	)
Examiner: William R.A. Jarvis	)
Attorney Docket No.: 6248.4	)

DECLARATION OF STEPHEN P. ARNERIC
PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Stephen P. Arneric, hereby declare that:

1. I have reviewed the above-captioned patent application and am familiar with the subject matter disclosed therein.

2. I have reviewed and am familiar with a U.S. Patent and Trademark Office (USPTO) official action dated October 10, 2001, in which the USPTO commented on the application.

3. On February 19, 2002, I participated in an interview at the USPTO with attorneys prosecuting the application (James J. Napoli and Sandip H. Patel) and the examiner responsible for reviewing the application (William R.A. Jarvis).

4. In 1979, I received a B.S. degree in Physical Science from the Lyman Briggs College at Michigan State University (East Lansing, MI), and in 1983, I received a Ph.D. in Pharmacology from the University of Iowa (Iowa City, IA).

5. From 1983 to 1985, I conducted post-doctoral research in the Department of Neurobiology/Cerebral Circulation at Cornell University Medical College (New York, NY). From 1985 to 1986, I was an Assistant Professor in the Department of Neurobiology at Cornell University Medical College.

From 1987 to February of 1998, I was employed by Abbott Laboratories (Abbott Park, IL), where I held the following positions: Research Investigator and Project/Group Leader for Cognitive Function (1989 to 1991); Project Leader for Cholinergic Channel Modulators in the Neuroscience Pharmaceutical Discovery Division (1991 to 1997); and, Director of Neurological and Urological Diseases Research in the Neuroscience Pharmaceutical Discovery Division (1997 to 1998).

From March of 1998 to May of 2000, I was a Senior Director in Central Nervous System (CNS) Research at DuPont Phramaceuticals Company (Wilmington, DE).

Since May of 2000, I have been employed by Pharmacia Corporation (Kalamazoo, MI) as a Director in Neurobiology and Central Nervous System (CNS) Discovery Research.

Additionally, since 1986, I have been employed by Southern Illinois University School of Medicine (Springfield, IL), where I have held the following positions: Assistant Professor (1986 to 1989); Adjunct Assistant Professor (1989 to 1992); Adjunct Associate Professor (1992 to 1996); and, Adjunct Professor (1996 to present).

6. Based on my academic and employment experiences, I am qualified to provide the comments set forth herein regarding the subject matter of the above-captioned application.

7. I have reviewed and am familiar with Max *et al.* (1991) *Pain* 45:3-10 (hereafter "the Max 1991 article").

8. Attached hereto are Tables I and II, which respectively set forth inhibition constants of compounds for various monoamine transporters and receptors, and the selectivity for the norepinephrine transporter over the serotonin transporter. The selectivity values reported in the last column of Table II are obtained by dividing the inhibition constant (K_i, nM) for serotonin by the inhibition constant (K_i, nM) for

norepinephrine. The selectivity value is a unitless number, where a value equal to one represents no selectivity (i.e., equal affinity for both transporters), values greater than one represent greater norepinephrine selectivity, and values less than one represent greater serotonin selectivity.

9. As reported in Table II, desipramine exhibits selectivity (430 fold) for the norepinephrine transporter site over that of the serotonin transporter site. In the 1991 Max article, Max et al. have suggested that blockade of norepinephrine reuptake, an action shared by desipramine, amitriptyline, and other antidepressants proven effective in neuropathic pain, may mediate the pain relief. In their study, Max et al. demonstrate the effective plasma levels required to produce pain relief in a majority of patients (13 of 18, or 72%) is in the range of 50 to 150 ng/ml. (See Figure 4 at p. 7 of the Max 1991 article.) This translates to a total plasma concentration of 188 to 540 nM, or approximately 9 to 28 nM, if one were to correct for the portion of free drug available to associate with the receptor, knowing the other portion is bound to plasma proteins. Based on Figure 4 of the Max 1991 article, there is a reasonable probability that a significant portion (approximately 50%) of the H_1 and α_1-adrenergic receptors would also be occupied at plasma concentrations that produce relief from neuropathic pain. Consequently, one cannot definitively conclude that desipramine produces relief from neuropathic pain by interacting solely at the norepinephrine transporter site.

10. The data reported in Tables I and II for (S,S) reboxetine stand in stark contrast to the corresponding data for desipramine. Specifically, (S,S) reboxetine exhibits surprisingly exceptional selectivity (>15,000) for the norepinephrine transporter over that of the serotonin transporter. See Table II. Consequently, and in contrast to desipramine, one can definitively conclude that compounds, such as (S,S) reboxetine, produce relief from chronic pain solely through their highly selective interaction with the norepinephrine transporter site.

11. Still further, the data reported in Table I conclusively shows that (S,S) reboxetine is a highly selective inhibitor of the norepinephrine transporter site having almost 25,000 fold selective response over other transporter/receptor sites (5-HT_{2A}, H_1, α_1-adrenergic, and muscarinic) believed to be responsible for adverse side effects. Such high selectivity is not exhibited by any of the comparative compounds. Thus, the

selectivity of compounds, such as (S,S) reboxetine, should provide an overall improved safety and tolerability far beyond that of conventional tricyclic antidepressants.

12. Values reported in Tables I and II for amitriptyline, desipramine, and fluoxetine were obtained from Table 3 in Owens *et al.* (1997) *J. Pharmacol. Exp. Ther.* 283:1305-1322.

13. Inhibition constants reported in Tables I and II for (S,S) reboxetine and for racemic reboxetine at the norepinephrine and serotonin receptor sites were determined as follows:

Materials

(a) All test compounds were obtained/made-available from commercial sources (Sigma, RBI) with the exception of reboxetine and its enatiomers, which were obtained from Pharmacia Research Compound Collection (Kalamazoo, MI). The following materials were used:

(i) [N-methyl-^{3}H]-nisoxetine (purchased from Amersham Life Science (Buckinghamshire, England)); and,

(ii) [N-methyl-^{3}H]-citalopram (purchased from Dupont New England Nuclear Products (Boston, MA)).

Binding Assays

(b) Male Sprague Dawley rats were decapitated, and the cerebral cortical tissue was removed and homogenized in nine volumes of ice cold 0.32 M sucrose using a rotating pestle on 50 setting (10 up and down strokes).

(c) The obtained homogenate was centrifuged at 1000 x *g* for 10 minutes at 4°C.

(d) A supernatant was collected and centrifuged at 20,000 x *g* for 20 minutes at 4°C.

(e) Following centrifugation, the protein pellet resulting from the centrifuging steps was re-suspended in a Kreb's Hepes Buffer pH-adjusted to 7.0, wherein the buffer contained 20 nM Hepes, 4.16 nM $NaHCO_3$, 0.44 nM

KH_2PO_4, 0.63 nM NaH_2PO_4, 127 mM NaCl, 5.36 mM KCl, 1.26 mM $CaCl_2$, and 0.98 mM $MgCl_2$.

(f) Aliquots (5 ml each) were subsequently frozen and stored at -80°C; when needed, the aliquots were thawed at room temperature, and diluted to a final protein concentration of 30-150 µg of protein per well (or test tube) using the Kreb's Hepes Buffer.

(g) Four-hundered microliter (µl) aliquots of homogenate and 50 µl aliquots of both the radioligand and the test compound were added to each test volume for a total volume of 500 µl.

(h) The [N-methyl-^{3}H]-nisoxetine binding assay was incubated for two hours at 25°C. The nonspecific binding was defined by using 10 µM desipramine.

(i) The [N-methyl-^{3}H]-citalopram binding assay was incubated for one hour at 25°C. The nonspecific binding was defined by using 100 µM fluoxetine.

(j) The reactions were terminated by rapid vacuum filtration through Whatman GF/B glass-fiber filters (pre-soaked in buffer containing 0.5% polyethylenimine for approximately four hours) mounted on a Brandel cell harvester (Model MP48).

(k) The filters were washed rapidly three times using three milliliter aliquots of ice cold 0.9% saline.

(l) The filters were subsequently assayed for radioactivity by liquid scintillation counting.

Uptake Assays

(m) Uptake assays were performed using Madin-Darby canine kidney (MDCK) cell lines stably transfected with hNET, hDAT, or hSERT using conventional methods. See e.g., Wong *et al.* (2000) *Biol. Psychiatry* 47:818-29.

(n) Cells plated in a 96-well harvester were washed with Krebs-Ringer-Hepes buffer two days following plating and preincubated at room temperature with test drugs for five to ten minutes prior to addition of radiolabled substrates

([^{3}H]dopamine for hNET and hDAT cells, [^{3}H]serotonin for hSERT cells; all concentrations below 75 nM or 1/10 of respective substrate Kt values).

(o) Incubation for ten minutes is terminated by removal of supernatant and two washes of the cells with the same buffer.

(p) A scintillation cocktail was added to each well and the plates were counted using a Wallac MicroBeta scintillation counter at an efficiency of approximately 35%. Eleven to twelve concentrations of inhibitor (with two or four replicates) in the range of 100 pM to 1 mM were used in each assay.

(q) Identical drug dilutions were used on any day to assay plates of hNET, hDAT, and hSERT MDCK cells in parallel.

(r) Levels of nonspecific uptake are defined with 10 μM nomifensine (hNET and hDAT), 10 μM citalopram (hSERT), or with 100 μM cocaine.

(s) Uptake velocities were normalized to control conditions in each experiment, and the obtained data were analyzed with GraphPad Prism 3.0a using the four parameter logistic equation in which the maximal value is allowed to float.

14. Except where otherwise noted in the Tables, the inhibition constants reported in Tables I and II for (S,S) reboxetine and for racemic reboxetine at the 5-HT_{2A}, H_1, α_1-adrenergic, and Muscarinic transporter/receptors sites were determined using standard protocols established by Cerep (Le Bois L'Eveque, BP1, 86 600 Celle l'Evescault, FRANCE), and the following radioligands:

(a) [^{3}H]-ketanserin for the 5-HT_{2A} site;

(b) [^{3}H]-pyrilamine for the H1 site;

(c) [^{3}H]-prazosin for the α_1-adrenergic site; and,

(d) [^{3}H]-pirenzepine, [^{3}H]-methoctamine, [^{3}H]-4-DAMP for the respective M1, M2, and M3-M5 Muscarinic sites.

15. The techniques/assays set forth in the preceding paragraphs and in Owens *et al.* (1997) *J. Pharmacol. Exp. Ther.* 283:1305-1322, to obtain the data reported in the

attached Tables I and II are standard receptor binding techniques and functional reuptake assays.

16. These techniques and assays are amenable to high throughput screening (HTS) technologies that use robotics to automate handling and dilutions of compounds, and can be performed by one skilled in the art of HTS to identify compounds with potential for phramaceutical applications.

17. Although it was surprising and unexpected that (S,S) reboxetine exhibits remarkably greater selectivity for the norepinephrine transporter than it does for the serotonin transporter, it would be possible to search for such compounds using HTS technologies without undue experimentation.

18. Furthermore, it is entirely conceivable that up to 500,000 novel compounds could be screened within a three-month time period for their ability to selectively interact with the norepinephrine transporter.

(a) One such HTS screening process could be performed at a single concentration (1 μM) and examine the ability of the screening compound to displace [N-methyl-^{3}H]-nisoxetine, a relatively selective ligand for the norepinephrine transporter , from rat brain membrane preparations.

(b) Compounds found to be active would be confirmed by completeing a full concentration-response curve, and the initial selectivity against the serotonin transporter would be confirmed using [N-methyl-^{3}H]-citalopram, a relatively selective serotonin ligand.

(c) The functional nature of these interactions with human recombinant norepinephrine, serotonin, and DAT transporter sites could be confirmed in secondary screening assays.

19. All statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 U.S.C. § 1001 and may jeopardize the validity of the application or any patent which may issue thereon.

March 22, 2002

Stephen P. Arneric

TABLE I. Inhibition Constants (K_i, nM) of Compounds for Various Monoamine Transporter and Receptor Sites

Site	Norepinephrine	Serotonin	5-HT_{1A}	H_1	α_1-adrenergic	Muscarinic
(*S*,*S*) Reboxetine	0.21 ± 0.03	>3000	>5000	>5000	>5000	>5000
Racemic Reboxetine	1.04 ± 0.20	134 ± 11.5	>1000	312[a]	>5000[a]	>5000[a]
Amitriptyline [a]	8.6 ± 0.04	16 ± 0.8	5.3 ± 0.2	0.17 ± 0.01	4.4 ± 0.2	2.6 ± 0.1
Desipramine [a]	0.31 ± 0.01	129 ± 7	115 ± 13	31 ± 1	23 ± 1	37 ± 1
Fluoxetine [a]	473 ± 11	2.0 ± 0.1	141 ± 9	933 ± 23	1353 ± 17	512 ± 12

TABLE II. Selectivity for the Norepinephrine Transporter Over the Serotonin Transporter

Site	Norepinephrine (K_i, nM)	Serotonin (K_i, nM)	Selectivity [c] for Serotonin (K_i)/Norepinephrine (K_i)
(+)-[*S*,*S*]-Reboxetine	0.21 ± 0.03	>3000	**>15,000**
Racemic Reboxetine	1.04 ± 0.20	134 ± 11.5	**129**
Amitriptyline [b]	8.6 ± 0.04	16 ± 0.8	**1.8**
Desipramine [b]	0.3 ± 0.01	129 ± 7	**430**
Fluoxetine [b]	473 ± 11	2 ± 0.1	**0.004**

a Values were obtained from Table 19-3 in R.J. Baldessarini, Depression and Mania, *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th Ed., Chapter 19, pp. 447-483, (2001).

b Values were obtained from Table 3 in Owens *et al.* (1997) *J. Pharmacol. Exp. Ther.* 283:1305-1322.

c Unit-less values were calculated by dividing the K_i value for the serotonin transporter site by the K_i value for the norepinephrine transporter site.

APPENDIX "B"

Copy of a "Statutory Declaration" of Dr. Sian Louise Ratcliffe filed in the European Patent Office during prosecution of European patent application No. 00941659.5, which is the European regional phase of the international counterpart to the current application.

In the matter of European Patent Application no. 00941659.5

STATUTORY DECLARATION

I, Dr. Sian Louise Ratcliffe, of Preston, Kent, England, hereby solemnly and sincerely declare as follows:

1. I have a BSc (Hons) in Physiology and Pharmacology from the University of Southampton (1992) and a PhD in Pharmacology from the University of Cambridge (1996).

2. I was awarded an Oncological Foundation Scholarship in 1994 for my research into photodynamic therapy for pancreatic cancer.

3. Since completing my PhD in 1996, I have held academic and post-doctoral research posts in the Department of Pharmacology at the University of Cambridge. I was also Senior Lecturer and Examiner in Pharmacology and Dean of Preclinical Studies at Kigezi International School of Medicine, Cambridge Campus, UK.

4. Since 2000, I have worked for Pfizer Limited of Ramsgate Road, Sandwich, Kent, UK, in Worldwide Development. As a Global Clinical Submission Leader, Regulatory Project Leader and Global Safety Leader at Pfizer between 2000 and 2004, I was responsible for clinical safety assessment for a number of successful European centralised and national approvals in the Neuropsychiatry therapeutic area and, in particular, I was responsible for developing and communicating risk/benefit arguments for novel psychiatry and neuropathic pain treatments.

5. I am currently Director, Safety Risk Management Lead, in the Safety and Risk Management Department. I am responsible for coordinating the development of risk management strategies and plans for a number of products in Pfizer's Neuroscience portfolio, working across both exploratory and late clinical development phases.

6. I have performed the following qualitative safety review that has revealed an unexpected potential tolerability benefit/difference of S,S-reboxetine (ssRBX) in a chronic pain population, as compared with racemic reboxetine (RBX; EDRONAX®).

7. Following my review and summary based on data available to date, I consider that ssRBX is associated with an unexpected lower tachycardia adverse event frequency in chronic pain patients with post-herpetic neuralgia (PHN) compared with racemic

reboxetine (RBX) used at equivalent doses to treat an equivalent elderly patient population with major depressive disorder (MDD).

The lower tachycardia reporting rate in PHN patients treated with ssRBX compared with that in depression patients treated with RBX is unexpected because:

1) it is well-documented that background rates of tachycardia increase with age and therefore a higher rate of tachycardia would be expected given the elderly nature of the PHN patient population as compared to the MDD population; and

2) elderly PHN patients were exposed to equivalent doses of ssRBX as compared with elderly MDD patients treated with RBX, and a similar rate of tachycardia reporting would therefore be expected.

Furthermore, the lower than expected frequency of tachycardia is surprising based on prior publication of racemic reboxetine study data suggesting that ssRBX is responsible for the hemodynamic effects of reboxetine in humans. The reduced tachycardia frequency of ssRBX is further unexpected based also on prior evidence that the S,S-enantiomer is the more potent of the two RBX enantiomers at the norepinephrine transporter (NET).

The lower frequency of palpitations/tachycardia is of clinical importance, given that some patients with chronic pain may well have autonomic neuropathy (eg. in diabetic painful neuropathy [DPN]), which is associated with a higher background rate of palpitations. This finding constitutes an unexpected benefit of ssRBX in the chronic pain patient population.

8. The following detailed analysis was performed.

8.1 Details of RBX studies in elderly patients

In the RBX clinical programme for major depressive disorder (MDD), four studies were conducted in elderly (>65 years old) patients. The majority of studies in the RBX clinical programme were conducted in the 18-65 year age range (N=1825 overall treated with RBX).

Three short-term studies were conducted in the elderly– one of which was discontinued early (**Study 032**, placebo-controlled); and two completed – **Study 035** was active-controlled and **Study 019** was open-label. A long-term open-label study was also conducted (**Study 034**). In the three completed elderly depression studies, 388 patients were evaluable for safety. See Appendices 1 to 4 for study details.

8.2 Details of ssRBX study in post herpetic neuralgia

To date, the ssRBX clinical programme for neuropathic pain comprises one study in post herpetic neuralgia (PHN) in patients who were gabapentin treatment failures (Study 1001). The study was conducted in a predominantly elderly population (mean patient age of 68 years), with 42% of patient being over the age of 75, and a total number of 98 patients treated with ssRBX. The study was conducted in a short-term 5-week,

double-blind placebo controlled multicentre treatment setting. See Appendix 5 for further study details.

8.3 Comparison of overall safety data from RBX/ssRBX studies

The adverse event profiles for RBX (from Phase 2/3 major depressive disorder studies) and ssRBX from a chronic pain population (post-herpetic neuralgia study 1001) are summarized in Table 1 below. Of note, tachycardia was reported at nearly four times the frequency on RBX as compared with ssRBX (4% vs 1%) and the term palpitation(s) was reported more frequently on RBX (2%) compared with ssRBX (0%). Further differences are noted in the placebo-corrected frequency of dry mouth, with twice as much reported on RBX compared with ssRBX (20% vs 12%); three times the frequency of hyperhidrosis/sweating was noted with RBX compared with ssRBX (9% vs 3%) and twice the frequency of anorexia/loss of appetite was noted with RBX compared with that seen on ssRBX (4% vs 2%).

The initial qualitative analysis has some limitations in interpretation based on the differences in sample sizes – comparing a sample of 98 patients treated with ssRBX to a sample of 1825 patients treated with RBX. In addition, although equivalent doses of ssRBX have been studied for similar treatment periods (6-8 weeks with RBX and 5 weeks with ssRBX), the age ranges of the populations are different. RBX was studied predominantly in 18-65 year olds and the ssRBX PHN study was conducted in predominantly elderly patients (majority >65 years). Therefore, further descriptive analyses have been conducted specifically with the elderly RBX studies to assess an age-matched group and a more balanced population sample for comparisons.

Table 1. Treatment-Emergent All Causality Adverse Events (≥2% Incidence) for patients administered RBX vs. ssRBX

Adverse Event	RBX studies 4-10mg/day All terms are COSTART			ssRBX 1-6mg/day All terms are MedDRA		
	RBX (n = 1825) n (%)	Placebo (N=1248) n (%)	RBX AE frequency Placebo-corrected	ssRBX AE frequency Placebo-corrected	ssRBX (N=98) n (%)	Placebo (N=108) n (%)
Constipation	376 (20.6)	87 (7.0)	13.6	19.8	23 (23.5)	4 (3.7)
Dizziness	209 (11.5)	82 (6.6)	4.9	14.4	16 (16.3)	2 (1.9)
Dry Mouth	611 (33.5)	167 (13.4)	20.1	12.4	14 (14.3)	2 (1.9)
Insomnia	391 (21.4)	123 (9.9)	11.5	8.4	11 (11.2)	3 (2.8)
Dysuria*	81 (4.4)	6 (0.5)	3.9	7.3	8 (8.2)	1 (0.9)
Nausea	228 (12.5)	120 (9.6)	2.9	5.5	9 (9.2)	4 (3.7)
Hyperhidrosis#	248 (13.6)	56 (4.5)	9.1	3.2	5 (5.1)	2 (1.9)
Chest Pain	-	-	-	3.1	3 (3.1)	0
Anxiety	*87 (4.8)*	*67 (5.4)*	*-0.6*	2.2	3 (3.1)	1 (0.9)
Anorexia£	114 (6.2)	28 (2.2)	4.0	2.0	2 (2.0)	0 (0)
Asthenia	97 (5.3)	61 (4.9)	0.4	2.0	2 (2.0)	0
Urinary retention	48 (2.6)	6 (0.5)	1.9	2.0	2 (2.0)	0
Headache	*390 (21.4)*	*292 (23.4)*	*-2.0*	1.5	6 (6.1)	5 (4.6)
Pruritus	23 (1.3)	11 (0.9)	0.4	1.2	3 (3.1)	2 (1.9)
Somnolence	*78 (4.3)*	*72 (5.8)*	*-1.5*	1.2	3 (3.1)	2 (1.9)
Paraesthesia	65 (3.6)	27 (2.2)	1.4	1.1	2 (2.0)	1 (0.9)
Urinary hesitation♣	25 (1.4)	19 (1.5)	-0.1	1.0	1 (1.0)	0
Abnormality of accommodation^	65 (3.6)	22 (1.8)	1.8	1.0	1 (1.0)	0
Tachycardia$	87 (4.8)	12 (1.0)	3.8	1.0	1 (1.0)	0
Diarrhoea	*63 (3.5)*	*114 (9.1)*	*-5.6*	0.3	3 (3.1)	3 (2.8)
Vomiting	*56 (3.1)*	*43 (3.4)*	*-0.3*	0.1	1 (1.0)	1 (0.9)
Tremor	48 (2.6)	17 (1.4)	1.2	0.1	1 (1.0)	1 (0.9)
Agitation	43 (2.4)	19 (1.5)	0.9	-	-	-
Hypotension	25 (1.4)	12 (1.0)	0.4	-	-	-
Rhinitis	*34 (1.9)*	*33 (2.6)*	*-0.7*	-	-	-
Palpitations	67 (3.7)	22 (1.8)	1.9	-1.9	0 (0)	2 (1.9)

Source: RBX Integrated Summary of Safety; ssRBX 1001 Study report tables

*this was termed Urination impaired for the RBX studies; # this was termed Sweating for the RBX studies; ♣ this was termed Urinary frequency in the RBX studies; $ this was termed heart rate increased in ssRBX study; £ decreased appetite in ssRBX study; ^ vision blurred in ssRBX study

numbers in *italics* represent AEs at greater frequency in placebo group

Note that COSTART and MedDRA are different coding dictionaries for adverse event terms. These dictionaries are comparable for the purposes of this analysis.

8.4 Comparison of safety profiles for RBX and ssRBX in elderly patients

The safety data for RBX and ssRBX can be compared in elderly patients by viewing the adverse event profiles for comparable doses (Table 2). The PHN patients in Study 1001 treated with ssRBX received doses of 1-6mg/day ssRBX – equivalent to 2-12mg/day RBX (the S,S-enantiomer comprises 50% of the racemic mixture). Patients who were >75 years old received 1-3mg/day ssRBX (equivalent to 2-6mg/day racemic mixture) and patients <75 years old received 2-6mg/day ssRBX (equivalent to 4-12mg/day racemic mixture). Therefore, older (>75 year old) PHN patients treated with ssRBX received similar doses of the S,S-enantiomer to >65 year old patients treated with RBX in the MDD programme (2-8mg/day).

As the mean age in the ssRBX study 1001 and the RBX elderly studies are similar (~68 years on ssRBX and ~73 years on RBX), a comparison of the adverse event (AE) profile on ssRBX overall in Study 1001 versus the AE profile of racemic reboxetine in the elderly studies is also valid (see Table 3 for by-study comparison).

Most of the adverse events reported follow a similar pattern across the elderly MDD studies with RBX and the PHN study with ssRBX. However, it is apparent that the adverse events of tachycardia and palpitations are more prominent in the RBX studies, and are less frequent with ssRBX in the PHN patient study. Furthermore, from the racemic reboxetine studies, the event of tachycardia was dose limiting, preventing escalation of dose, and was frequently associated with discontinuation and lack of toleration of RBX (See Appendix 3, Study 019).

The lower tachycardia reporting rate in PHN patients treated with ssRBX compared with that in depression patients treated with RBX is unexpected because:

1) it is well-documented that background rates of tachycardia increase with age[a] and therefore a higher rate of tachycardia would be expected given the elderly nature of the PHN patient population as compared to the MDD population; and

2) elderly PHN patients were exposed to equivalent doses of ssRBX as compared with elderly MDD patients treated with RBX, and a similar rate of tachycardia reporting would therefore be expected.

In addition, an early study with RBX suggested that ssRBX is responsible for the hemodynamic and adverse effects of reboxetine in humans[b].

The lower frequency of palpitations/tachycardia reported in the current PHN study with ssRBX is expected to be of clinical importance in the chronic pain patient population, given that patients with chronic pain may well have autonomic neuropathy (ie in diabetic painful neuropathy [DPN]), which is associated with palpitations[c].

A further difference of note between ssRBX and RBX is the lower reporting rates of the autonomic adverse effects dry mouth and hyperhidrosis (increased sweating) in the PHN patient population. These side effects can be manifest in common conditions in diabetic patients with chronic pain, eg hyperglycemia (dry mouth) and autonomic neuropathy (sweating). The lower frequency of these autonomic events and lower rates of anorexia/decreased appetite with ssRBX compared with RBX are considered to be of clinical importance in chronic pain patients.

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[a] Background rates of tachycardias increase with age. Tachycardias, especially supraventricular tachycardia, have been reported with an incidence of 4.1% in elderly population. The incidence of sinus tachycardia has been estimated as 2.6% in elderly and 5.5% in ≥55-years-old subjects (Casiglia et al, 1993; Bartel et al, 1971). In a study by Yasumura et al, which included elderly subjects aged 79-81 years old, >10% of subjects presented some kind of arrhythmia, 2.4% had tachycardia, 2.2% atrial fibrillation and 1.9% bradycardia. The prevalence of other types of arrhythmia was estimated as 8.2%.

[b] Denolle et al, 1999.

[c] Adriansen et al, 2005)

Table 2.

Adverse Event Profile Comparison of ssRBX (<75 and >75 year olds) and RBX (>65 year olds) - Frequently (≥5%) Reported Adverse Events (All causality)

Adverse Event	PHN Patients				Depression/Dysthymia Patients					
	Study A606-1001 ≥75 years ssRBX 1-3mg/day N = 41		Study A606-1001 <75 years ssRBX 2-6mg/day N = 57		Study 034 >65 years RBX 4-8mg/day N=160		Study 035 >65 years RBX 4-6mg/day N=176		Study 019 >65 years RBX 2-8mg/day N=12	
	n	%	n	%	n	%	n	%	n	%
Constipation	11	27	12	21	9	6	31	18	-	-
Dry Mouth	9	22	5	9	14	9	39	22	-	-
Dizziness	8	19.5	8	14	2	1	-	-	-	-
Nausea	4	10	5	9	19	12	20	11	-	-
Insomnia	3	7	8	14	19	12	11	6	-	-
Flatulence	2	5	0	0	2	1	1	1	-	-
Decreased appetite	2	5	0	0	3	2	4	2	-	-
Dysuria	2	5	6	10.5	3	2	7	4	-	-
Increased sweating	2	5	3	5	8	5	16	9		-
Somnolence	1	2	4	7	-	-	4	2	-	-
Headache	1	2	5	9	16	10	11	6		-
AEs of note:										
Tachycardia/HR increased	0	0	1	2	9	6	3	2	5	42
Cardiac rhythm disorder*	-	-	-	-	2	2	2	1	4	33
Palpitation	0	0	0	0			2	1		
AV block	0	0	1	2	1	1	0	0	-	-

Source: ssRBX Study 1001 Ad Hoc Table 005C; Study 034 Table 16.3.1.2; Study 035 Table 48; Study 019 Table 12

* cardiac rhythm disorder comprises terms of extrasystoles/extrasystolic arrhythmia, atrial fibrillation and supraventricular tachycardia

Table 3.

Adverse Event Profile Comparison of ssRBX and RBX - Frequently (≥5%) Reported Adverse Events

Adverse Event	PHN Patients Study A606-1001 ssRBX 1-6mg/day N=98		Depression/Dysthymia Patients Study 034 RBX 4-8mg/day N=160		Study 035 RBX 4-6mg/day N=176		Study 019 RBX 2-8mg/day N=12	
	n	%	n	%	n	%	n	%
Constipation	23	22	9	6	31	18	-	-
Dizziness	16	16	2	1	-	-	-	-
Dry Mouth	14	13	14	9	39	22	-	-
Insomnia	11	11	19	12	11	6	-	-
Nausea	9	8	19	12	20	11	-	-
Dysuria	8	8	3	2	-	-	-	-
Headache	6	6	16	10	11	6	-	-
Increased sweating	5	5	8	5	16	9	-	-
Tachycardia/HR increased	1	1	9	6	3	2	5	42
Cardiac rhythm disorder	-	-	-	-	-	-	4	33

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10. The following Appendices are referred to in this Declaration:

APPENDIX 1

Table 4. Studies of RBX in Older Patients with MDD

Protocol	Location	Study Design	Treatment	Dose (mg/d)	N	Mean Age [Range]	Gender (M/F)
Placebo-Controlled Short-Term Study							
032*	Single Centre	Phase 2, DB, randomised,	RBX	4-6	24	80 [63-90]	5 / 19
			PBO	0	26	80 [72-89]	6 / 20
Jun 1991 – Nov 1991	Italy (PI = Andreoli)	PG, 8-wk PC study in hospitalised elderly (>65y) patients					
Active-Controlled Short-Term Study							
035	Multicentre	Phase 2, DB, randomised,	RBX	4-6	176	74 [56-90]	39 / 137
			IMI	75-100	171	75 [64-95]	45 / 126
Sept 1992 – May 1994	46 centres	PG 8-wk study in elderly (>65y) patients with MDD: RBX vs IMI					
	Europe						
	Australia						
	Brazil						
Open, Uncontrolled Short-Term Study							
019	Single Centre	Phase 2, OL, 4-wk, within patient dose escalation efficacy, safety and PK study in hospitalised elderly (>65y) patients	RBX	4	1	80 [75-87]	0 / 12
				6	2		
Nov 1990	Italy (PI = Andreoli)			8	9		
Completed Long-Term Study							
034	Multicentre	Phase 3, OL, uncontrolled 6-wk RBX run-in period, followed by OL 1-yr LT treatment period in elderly (>65y) patients who responded to RBX during run-in phase	RBX	4, 6 or 8	160	73 [64-92]	51 / 109
	18 centres		RBX	4, 6 or 8	139		
	Europe						
	Lat Am						

* Discontinued due to infrequent observation of study endpoint (decrease of ≥50% from baseline in HAM-D total score at last assessment) before planned 70 patients enrolled.

APPENDIX 2

Study 035 Multicenter, Multinational Double-Blind Study of the Tolerability and Activity of RBX versus Imipramine in Elderly Patients Suffering from Depressive Disorders

In Study 035, a total of 347 patients, aged over 65 years, with MDD or Dysthymia (DYS) received treatment with RBX (n=176; 109 with MDD and 67 with DYS) or imipramine (IMI; n=171; 109 with MDD and 62 with DYS) for 8 weeks. Patients were stratified by diagnosis and were then randomized to receive treatment with RBX (2 mg bid through the end of the third week) or IMI (25 mg bid from days 1 to 3 and then 25 mg in the morning and 50 mg in the evening from days 4 to 21). After 3 weeks of treatment, the daily doses of active treatment could be increased from 4 to 6 mg in the RBX-treatment group and from 75 to 100 mg in the IMI-treatment group.

The age range of patients in the study in the RBX treatment arm was 56–90 years, with a mean age of 73.80.

At least one treatment-emergent adverse event was reported in 68% (120/176) of the patients in the RBX-treatment group and in 71% (122/171) of the patients in the IMI-treatment group. Twelve serious adverse events were reported, 2 on RBX and 10 on IMI. No deaths were reported on RBX, although 4 were reported on IMI.

The most frequently reported (ie, reported in at least 5% of the patients in any treatment group) adverse events are presented in Table 5.

Table 5.

Study 035: Frequently (>5%) Reported AEs (All Causality) by Treatment Group

Adverse Event	Treatment Group	
	RBX 4-6mg/day N=176	Imipramine N=171
Dry Mouth	39 (22%)	39 (23%)
Constipation	31 (18%)	31 (18%)
Nausea	20 (11%)	17 (10%)
Increased Sweating	16 (9%)	15 (9%)
Headache	11 (6%)	9 (5%)
Insomnia	11 (6%)	5 (3%)
Urinary Tract Infection	6 (3%)	10 (6%)

Source: Study 035 Table 48

Forty-seven patients discontinued the study because of one or more adverse events; 20 (20/176; 11%) were in the RBX-treatment group and 27 (27/171; 16%) were in the IMI-treatment group.

APPENDIX 3

Study 019: Open Dose-Range Finding, Efficacy, Tolerability (and Pharmacokinetics) of RBX in Elderly Patients Suffering From Depressive Disorders

In Study 019, 12 elderly patients, aged over 65 years, who were hospitalized with MDD or DYS received treatment with increasing doses of RBX from 2 to 8 mg (the maximum-allowable daily dose in this population) for 4 weeks. Nine patients received the maximum-allowable daily dose of 8 mg. For one patient, who later was withdrawn from the study because of atrial fibrillation, the maximum daily dose was 4 mg. For 2 additional patients, the maximum daily dose was 6 mg; in these patients, escalation to the 8-mg dose was prevented by the development of tachycardia.

Treatment emergent adverse events, all of which were related to cardiac rhythm disorders, were reported in 4 of 12 (33%) patients. The 4 adverse events were cardiac rhythm-related disorders: severe atrial fibrillation associated with particularly elevated plasma levels of RBX, extrasystolic arrhythmia, tachycardia, and supraventricular tachycardia. From vital sign (heart rate) measurements, tachycardia (>100 beats/min) was the most frequent side effect, being reported in 5 patients (42%). Additionally, 1 report of a newly observed ECG abnormality (left ventricular hypertrophy with occasional ectopic beats) was recorded at the final assessment.

In conclusion, this study suggested that daily RBX doses should not exceed 6 mg in subsequent controlled studies of the efficacy and tolerability of RBX in elderly depressed patients.

Table 6.

Study 019: Adverse Events

Adverse Event	RBX N=12
Tachycardia (HR >100bpm)	5 (42%)
Cardiac Rhythm Disorders	4 (33%)
Tachycardia	1 (8%)
Atrial Fibrillation	1 (8%)
Extrasystolic arrythmia	1 (8%)
Supraventricular tachycardia	1 (8%)

Source: Study 019 Table 12

APPENDIX 4

Study 034: Multicenter, Multinational Open Study of the Tolerability and Activity of RBX in the Continuation Therapy of Depressive Disorder in Elderly Patients

In Study 034, a total of 160 patients, aged over 65 years, with MDD (n=95) or DYS (n=65) were treated with RBX, beginning with 4 mg daily (2 mg bid) from study days 1 to 14 and continuing either at the same dosage for the remainder of the 6-week run-in phase or increasing to 6 mg (2 and 4 mg doses) or to 8 mg (4 mg bid) daily. One hundred and thirty-nine patients who were responders during the run-in phase were eligible to continue treatment with the same dosage of RBX until relapse occurred or for a maximum period of 1 year. During the long-term phase of the study, 105 completed the long-term phase.

At least one treatment-emergent adverse event was reported in 76% (122/160) of the patients in the RBX group. Twenty-five patients discontinued the study prematurely because of one or more adverse events. Sixteen serious adverse events occurred in 14 patients during the study and 7 (4.3%) patients died. The most frequently reported (ie, reported in at least 5% of the patients in any treatment group) adverse events are presented in Table 4.

Table 7

Study 034: Frequently (≥5%) Reported Adverse Events

Adverse Event	RBX N=160
Insomnia	19 (12%)
Nausea	19 (12%)
Headache	16 (10%)
Dry Mouth	14 (9%)
Paraesthesia	9 (6%)
Constipation	9 (6%)
Diarrhoea	9 (6%)
Tachycardia	9 (6%)
Increased Sweating	8 (5%)
Fatigue	8 (5%)

Source: Study 034 Table 6.3.1.2

APPENDIX 5

Study 1001: A Five-Week, Randomised, Double-blind, Placebo-controlled Multicentre Study of [S,S]-reboxetine in Patients with Post Herpetic Neuralgia (PHN) who were Gabapentin (GBP) Treatment Failures.

Study 1001 was a five week, randomised, double-blind, placebo controlled, multi-centre study in 206 subjects with PHN, who were GBP treatment failures. ssRBX was clearly efficacious in the treatment of PHN in subjects who are GBP treatment failures.

The study comprised of three phases; a seven week screening phase which included four weeks of GBP treatment, a five week randomised double-blind treatment period, and a one week follow-up study period.

In total, 22 patients in the ssRBX treatment group and 2 patients in the placebo treatment group withdrew from the study due to treatment emergent adverse events. There were no deaths in the study. Four subjects reported serious adverse events: one subject reported syncope; the second subject had chest pain; one event of overdose of study medication (study site dispensed in error); and one subject had a chest pain, a kidney infection and angina. None of the events were considered related to treatment.

The most frequently reported all causality adverse events were constipation, dizziness, dry mouth, insomnia, nausea and headache. The majority of adverse events had resolved by the end of the study. The number of ongoing events was similar for each treatment group.

Table 8

Study 1001: Frequently Reported Adverse Events (>5%)

Adverse Event	[S,S]-RBX N=98	Placebo N=108
Constipation	23 (23.5%)	4 (4%)
Dizziness	16 (16%)	2 (2%)
Dry Mouth	14 (14%)	2 (2%)
Insomnia	11 (11%)	3 (3%)
Nausea	9 (9%)	4 (4%)
Dyspepsia	8 (8%)	1 (1%)
Headache	6 (6%)	5 (5%)

Source: Study 1001 Table 13.6.2.3

And I make this solemn declaration conscientiously believing the same to be true and by virtue of the provisions of the Statutory Declarations Act 1835.

Declared at Sandwich in the county of Kent in England this 23rd day of September, 2005 by

Sian Louise Ratcliffe

before me

Notary Public

Andrew Martin Johnson B.A.
NOTARY PUBLIC
29 St. George's Place
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315/2005.

APPENDIX "C"

Copy of Rosner et al. (**1996**) *Clin. J. Pain* **12**:56-58.

The Clinical Journal of Pain
12:56–58 © 1996 Lippincott–Raven Publishers, Philadelphia

Case Report

Gabapentin Adjunctive Therapy in Neuropathic Pain States

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Abstract:

Objective: This is a report of a trial of the new antiepileptic agent gabapentin in patients with intractable neuropathic pain.

Design: A case series of patients with a diagnosis of neuropathic pain whose previous management was inadequate were given oral gabapentin in increasing doses and were followed for a minimum of 2 months, monitored for efficacy and side effects.

Setting: An outpatient pain management center located within a major university medical center.

Patients: Convenience sample of patients referred for management of intractable neuropathic pain.

Interventions: Simplification of existing pharmacologic management, addition of gabapentin, and attempted reduction of opiate analgesic doses.

Main Outcome Measures: Patient self-reports and pain scores in successive office visits.

Results: Gabapentin provides analgesic activity for patients with neuropathic pain and has the advantage of a low side effect profile and drug toxicity.

Key Words: Gabapentin—Neuropathic pain—Antiepileptic drugs.

Pain secondary to injuries or disease states of the peripheral or central nervous system is often resistant to management (1). Advocated treatment modalities have included nerve blocks, transcutaneous nerve stimulation, and drug therapy, which is often limited by side effects. Gabapentin, a new antiseizure drug, was recently introduced as an adjunctive therapeutic agent for refractory epilepsy (2) and offers the advantage of relatively low toxicity and side effect profile, although it has yet to be demonstrated clinically effective in management of neuropathic pain. A letter has been published describing its successful use in one case of reflex sympathetic dystrophy (3). We felt that wider clinical use of gabapentin was warranted for management of other difficult neuropathic pain states that have been resistant to treatment. We report four such patients.

Manuscript submitted June 14, 1995; first revision received August 22, 1995; second revision received November 28, 1995; accepted for publication January 3, 1996.

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CASE REPORTS

Case 1

The patient is a 78-year-old woman with a long history of deafferentation neuropathy of the face. At the time of the trial, the patient's medication regimen was simplified to include only doxepin 300 mg/day, oxycodone 20 mg/day, and clonazepam 1.5

mg/day. Gabapentin was then added at 200 mg/day, advancing over the next 4 weeks to 500 mg/day (in divided doses). After 6 weeks of therapy, the patient reported good relief of her facial pain and oxycodone was slowly tapered and discontinued. After 6 months, the patient continues to report good relief with minimal sedating side effects on a regimen of gabapentin, clonazepam, and doxepin.

Case 2

The patient is a 50-year-old woman who presented 3 years after herniation of the L3-4 and L4-5 disks with sciatic-type pain in both legs. This pain complaint resolved, but with its resolution, she began complaining of burning pain in both legs diagnosed as mixed sympathetically maintained and sympathetically independent pain after positive phentolamine infusion. At the time of the trial, drug therapy of nortriptyline 50 mg/day and morphine sulfate sustained release 90 mg/day and epidural injections were ineffective. Gabapentin 100 mg t.i.d. was added, advancing over the next 2 weeks to 900 mg/day in divided doses. After 2 weeks, she reported increased pain relief and level of activity. After 2 months, she was able to walk on her own without support. After 4 months, she continues to report good pain relief on the combination of gabapentin, sustained release morphine, and nortriptyline.

Case 3

The patient is an 82-year-old man with multiple medical problems with a 10-year hiatus of postherpetic neuralgia with disabling episodes of lancinating pain, severe burning, and hyperesthesia of the left C2-4 dermatomes. Gabapentin 100 mg at bedtime was added to his opioid therapy (transdermal fentanyl 25 μg/h), advanced to 100 mg t.i.d. over 1 month. The dose could not be advanced above 300 mg/day because of dysequilibrium. On this dose the patient described diminished burning pain with minimal sedating side effects after 1 month. He still describes hypersensitivity and some lancinating episodes; however, their frequency has diminished. After 3 months of therapy, he continues to use the transdermal fentanyl and has better pain control with fewer side effects than with his previous management protocols.

Case 4

The patient is a 38-year-old HIV-positive man with bilateral lower-extremity HIV-related neuropathy, inadequately managed with amitriptyline 25 mg q.h.s. and oxycodone 5 mg q.i.d. Clonazepam 1 mg b.i.d. was started, which provided good relief of his burning but excessive sedation. His dose was reduced to 0.5 mg b.i.d. and his sedation diminished, but his burning pain returned. Gabapentin 100 mg t.i.d. was added, and after 2 weeks, he reported equivalent analgesia as with 2 mg/day clonazepam with no dysequilibrium or sedation. At follow-up visits 1 and 2 months later, he continues to report satisfactory relief of his burning pain. The oxycodone was stopped, and the patient continues to take amitriptyline, clonazepam, and gabapentin.

DISCUSSION

Anticonvulsant drugs exert their actions on the nervous system through two general mechanisms. They can reduce or prevent pathologically altered neurons from excessive discharge, and they can reduce the spread of excitation from abnormal foci to normal neurons. These drugs decrease membrane excitability by their interactions with ion channels or neurotransmitter receptors. Phenytoin, carbamazepine, and valproic acid decrease high-frequency repetitive firing of action potentials by enhancing sodium channel inactivation. Clonazepam and phenobarbital enhance γ-aminobutyric acid A (GABA-A) receptor-mediated inhibition (4). Gabapentin was designed to be an analogue of (GABA). Although the mechanism of action of gabapentin is unclear, it appears to bind to specific sites unevenly distributed through the brain. The highest concentration of these binding sites was in the cerebral cortex and the lowest in the white matter. This binding site appears to be localized to neuronal cell bodies in regions of the brain associated with excitatory amino acid input (5).

Although the etiologies of neuropathic pain syndromes are varied, the underlying pathological characteristics seem to include some abnormal activation of neurons within the nociceptive system (1). Medications that reduce pathologically altered neurons from excessive discharge would seem to be good choices for management of these syndromes. Anticonvulsants have therefore been advocated in management of refractory neuropathic pain, by virtue of their pharmacologic properties. One of the major limiting factors in their use is the high incidence of side effects, including sedation and disequilibrium (6). Gabapentin has a much lower incidence of side effects than other anticonvulsants (7)

and, from these cases, appears to have some analgesic effect in neuropathic pain states. Further study is warranted to determine the optimal dosing range and overall effectiveness.

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APPENDIX "D"

Product insert for Neurontin®, NDA 21-397, pp. 3-35, copyrighted 1998-'02 (Electronic record signed May 24, 2002).

Neurontin® (gabapentin) Capsules
Neurontin® (gabapentin) Tablets
Neurontin® (gabapentin) Oral Solution

DESCRIPTION

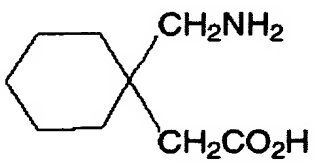
Neurontin® (gabapentin) Capsules, Neurontin® (gabapentin) Tablets, and Neurontin® (gabapentin) Oral Solution are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 mg and 800 mg of gabapentin or an oral solution containing 250 mg/5 mL of gabapentin.

The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400 mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C Blue No. 2 and titanium dioxide.

The inactive ingredients for the tablets are poloxamer 407, copolyvidonum, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, candelilla wax and purified water. The imprinting ink for the 600 mg tablets contains synthetic black iron oxide, pharmaceutical shellac, pharmaceutical glaze, propylene glycol, ammonium hydroxide, isopropyl alcohol and n-butyl alcohol. The imprinting ink for the 800 mg tablets contains synthetic yellow iron oxide, synthetic red iron oxide, hydroxypropyl methylcellulose, propylene glycol, methanol, isopropyl alcohol and deionized water.

The inactive ingredients for the oral solution are glycerin, xylitol, purified water and artificial cool strawberry anise flavor.

Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. The structural formula of gabapentin is:



Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice (e.g., spinal nerve ligation models, streptozocin-induced diabetes model, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test). Gabapentin did not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase, acetic acid abdominal constriction test, footpad heat irradiation test). The relevance of these models to human pain is not known.

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 μM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has

been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

Pharmacokinetics and Drug Metabolism

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability: Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution: Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58±6 L (Mean ±SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination: Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see Special Populations: Patients With Renal Insufficiency, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see DOSAGE AND ADMINISTRATION, Table 5).

Special Populations: *Adult Patients With Renal Insufficiency:* Subjects (N=60) with renal insufficiency (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 mL/min) to 52 hours (creatinine clearance <30 mL/min) and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min.

Dosage adjustment in adult patients with compromised renal function is necessary (see DOSAGE AND ADMINISTRATION). Pediatric patients with renal insufficiency have not been studied.

Hemodialysis: In a study in anuric subjects (N=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Disease: Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

Age: The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function. (See PRECAUTIONS, Geriatric Use, and DOSAGE AND ADMINISTRATION.)

Pediatric: Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day given TID. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day. (See DOSAGE AND ADMINISTRATION.)

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Postherpetic Neuralgia

Neurontin® was evaluated for the management of postherpetic neuralgia (PHN) in 2 randomized, double-blind, placebo-controlled, multicenter studies; N=563 patients in the intent-to-treat (ITT) population (Table 1). Patients were enrolled if they continued to have pain for more than 3 months after healing of the herpes zoster skin rash.

Table 1. Controlled PHN Studies: Duration, Dosages, and Number of Patients

Study	Study Duration	Gabapentin (mg/day)[a] Target Dose	Patients Receiving Gabapentin	Patients Receiving Placebo
1	8 weeks	3600	113	116
2	7 weeks	1800, 2400	223	111
		Total	336	227

[a] Given in 3 divided doses (TID)

Each study included a 1-week baseline during which patients were screened for eligibility and a 7- or 8-week double-blind phase (3 or 4 weeks of titration and 4 weeks of fixed dose). Patients initiated treatment with titration to a maximum of 900 mg/day gabapentin over 3 days. Dosages were then to be titrated in 600 to 1200 mg/day increments at 3- to 7-day intervals to target dose over 3 to 4 weeks. In Study 1, patients were continued on lower doses if not able to achieve the target dose. During baseline and treatment, patients recorded their pain in a daily diary using an 11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). A mean pain score during baseline of at least 4

was required for randomization (baseline mean pain score for Studies 1 and 2 combined was 6.4). Analyses were conducted using the ITT population (all randomized patients who received at least one dose of study medication).

Both studies showed significant differences from placebo at all doses tested.

A significant reduction in weekly mean pain scores was seen by Week 1 in both studies, and significant differences were maintained to the end of treatment. Comparable treatment effects were observed in all active treatment arms. Pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses. Figures 1 and 2 show these changes for Studies 1 and 2.

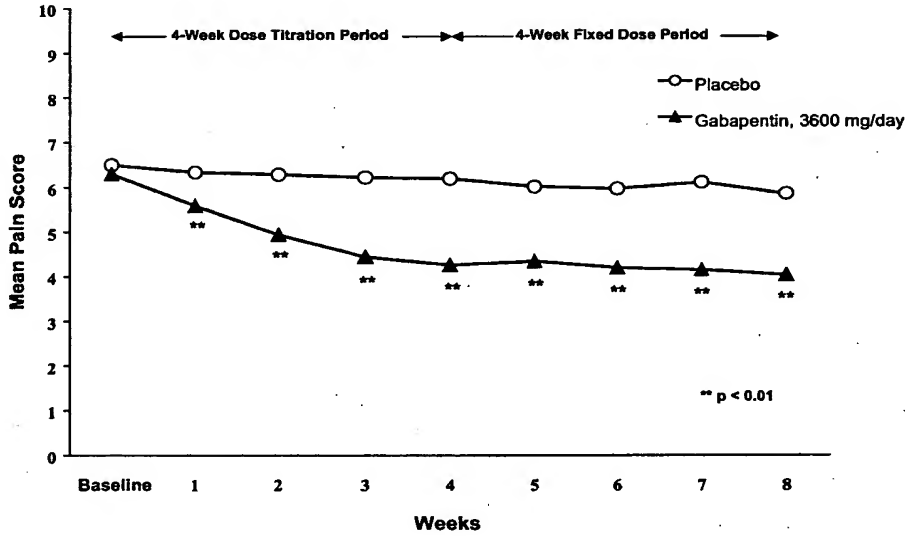


Figure 1. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 1

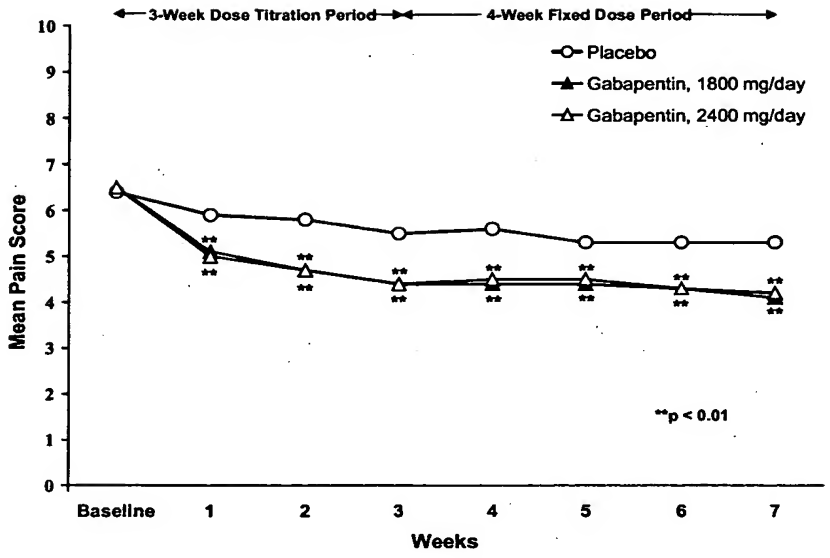


Figure 2. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 2

The proportion of responders (those patients reporting at least 50% improvement in endpoint pain score compared with baseline) was calculated for each study (Figure 3).

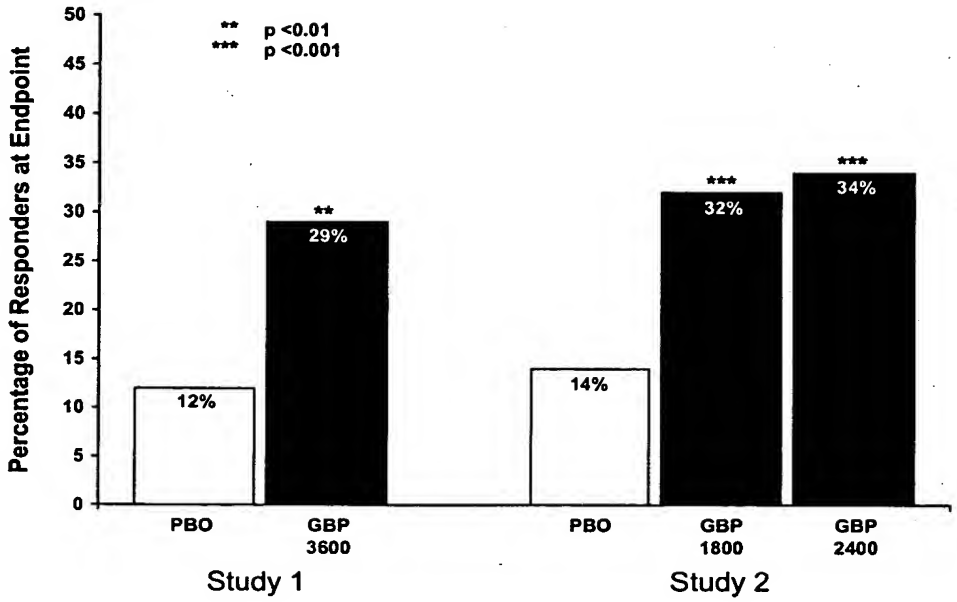


Figure 3. Proportion of Responders (patients with ≥50% reduction in pain score) at Endpoint: Controlled PHN Studies

Epilepsy

The effectiveness of Neurontin® as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, Neurontin® or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as (T - B)/(T + B), where B is the patient's baseline seizure frequency and T is the patient's

seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared Neurontin® 1200 mg/day divided TID with placebo. Responder rate was 23% (14/61) in the Neurontin® group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the Neurontin® group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day divided TID Neurontin® (N=101) with placebo (N=98). Additional smaller Neurontin® dosage groups (600 mg/day, N=53; 1800 mg/day, N=54) were also studied for information regarding dose response. Responder rate was higher in the Neurontin® 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the Neurontin® 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ($p = 0.224$). A better response was seen in the Neurontin® 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared Neurontin® 900 mg/day divided TID (N=111) and placebo (N=109). An additional Neurontin® 1200 mg/day dosage group (N=52) provided dose-response data. A statistically significant difference in responder rate was seen in the Neurontin® 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the Neurontin® 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day Neurontin® (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of Neurontin® on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for Neurontin® compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N=162, Neurontin®; N=89, placebo) also showed a significant advantage for Neurontin® over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of Neurontin® was used. Within each study the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 4).

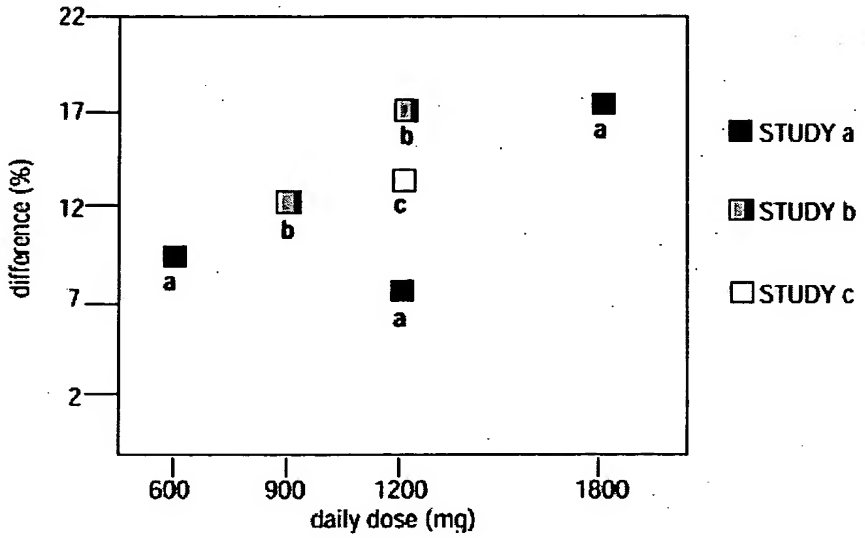


Figure 4. Responder Rate in Patients Receiving Neurontin® Expressed as a Difference From Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥12 Years of Age With Partial Seizures

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to Neurontin®. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups.

A fourth study in pediatric patients age 3 to 12 years compared 25 - 35 mg/kg/day Neurontin® (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the Neurontin® group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for Neurontin® (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day Neurontin® (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 72 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either the response ratio or responder rate.

INDICATIONS AND USAGE

Postherpetic Neuralgia

Neurontin® (gabapentin) is indicated for the management of postherpetic neuralgia in adults.

Epilepsy

Neurontin® (gabapentin) is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Neurontin® is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 - 12 years.

CONTRAINDICATIONS

Neurontin® is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Neuropsychiatric Adverse Events—Pediatric Patients 3-12 years of age

Gabapentin use in pediatric patients with epilepsy 3-12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school

performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3-12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving Neurontin® was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with Neurontin® across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with Neurontin® is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with Neurontin®.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.) The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and pre-existing tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of Neurontin®. Without knowledge of the background incidence and recurrence in a similar population

not treated with Neurontin®, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

Sudden and Unexplained Death in Patients With Epilepsy

During the course of premarketing development of Neurontin® 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving Neurontin® (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the Neurontin® program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the Neurontin® cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients

Patients should be instructed to take Neurontin® only as prescribed.

Patients should be advised that Neurontin® may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on Neurontin® to gauge whether or not it affects their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Neurontin® or morphine should be reduced appropriately (see Drug Interactions).

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin®. The value of monitoring gabapentin blood concentrations has not been established. Neurontin® may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 μg/mL; 1 mM) was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 μg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin: In a single (400 mg) and multiple dose (400 mg TID) study of Neurontin® in epileptic patients (N=8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg TID; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg TID; N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg TID; N=12) are identical whether the drugs are administered alone or together.

Naproxen: Coadministration (N=18) of naproxen sodium capsules (250 mg) with Neurontin® (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

Hydrocodone: Coadministration of Neurontin® (125 to 500 mg; N=48) decreases hydrocodone (10 mg; N=50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg Neurontin® and 21% to 22% lower, respectively, after administration of 500 mg Neurontin®. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

Morphine: A literature article reported that when a 60-mg controlled release morphine capsule was administered 2 hours prior to a 600-mg Neurontin® capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see PRECAUTIONS). Morphine pharmacokinetic parameter values were not affected by administration of Neurontin® 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine: In the presence of cimetidine at 300 mg QID (N=12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptives: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg TID; N=13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®): Maalox reduced the bioavailability of gabapentin (N=16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox. It is recommended that gabapentin be taken at least 2 hours following Maalox administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Drug/Laboratory Tests Interactions

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m^2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers

Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, Neurontin® should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use

Safety and effectiveness of Neurontin® (gabapentin) in the management of postherpetic neuralgia in pediatric patients have not been established.

Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established (see CLINICAL PHARMACOLOGY, Clinical Studies).

Geriatric Use

The total number of patients treated with Neurontin® in controlled clinical trials in patients with postherpetic neuralgia was 336, of which 102 (30%) were 65 to 74 years of age, and 168 (50%) were 75 years of age and older. There was a larger treatment effect in patients 75 years of age and older compared with younger patients who received the same dosage. Since gabapentin is almost exclusively eliminated by renal excretion, the larger treatment effect observed in patients ≥75 years may be a consequence of increased gabapentin exposure for a given dose that results from an age-related decrease in renal function. However, other factors cannot be excluded. The types and incidence of adverse events were similar across age groups except for peripheral edema and ataxia, which tended to increase in incidence with age.

Clinical studies of Neurontin® in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients (see CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Postherpetic Neuralgia

The most commonly observed adverse events associated with the use of Neurontin® in adults, not seen at an equivalent frequency among placebo-treated patients, were dizziness, somnolence, and peripheral edema.

In the 2 controlled studies in postherpetic neuralgia, 16% of the 336 patients who received Neurontin® and 9% of the 227 patients who received placebo discontinued treatment because of an adverse event. The adverse events that most frequently led to withdrawal in Neurontin®-treated patients were dizziness, somnolence, and nausea.

Incidence in Controlled Clinical Trials

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 1% of Neurontin®-treated patients with postherpetic neuralgia participating in placebo-controlled trials and that were numerically more frequent in the Neurontin® group than in the placebo group. Adverse events were usually mild to moderate in intensity.

Table 2. Treatment-Emergent Adverse Event Incidence in Controlled Trials in Postherpetic Neuralgia (Events in at least 1% of Neurontin®-Treated Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Preferred Term	Neurontin® N=336 %	Placebo N=227 %
Body as a Whole		
Asthenia	5.7	4.8
Infection	5.1	3.5
Headache	3.3	3.1
Accidental injury	3.3	1.3
Abdominal pain	2.7	2.6
Digestive System		
Diarrhea	5.7	3.1
Dry mouth	4.8	1.3
Constipation	3.9	1.8
Nausea	3.9	3.1
Vomiting	3.3	1.8
Flatulence	2.1	1.8
Metabolic and Nutritional Disorders		
Peripheral edema	8.3	2.2
Weight gain	1.8	0.0
Hyperglycemia	1.2	0.4
Nervous System		
Dizziness	28.0	7.5
Somnolence	21.4	5.3
Ataxia	3.3	0.0
Thinking abnormal	2.7	0.0
Abnormal gait	1.5	0.0
Incoordination	1.5	0.0
Amnesia	1.2	0.9
Hypesthesia	1.2	0.9
Respiratory System		
Pharyngitis	1.2	0.4
Skin and Appendages		
Rash	1.2	0.9
Special Senses		
Amblyopia[a]	2.7	0.9
Conjunctivitis	1.2	0.0
Diplopia	1.2	0.0
Otitis media	1.2	0.0

[a] Reported as blurred vision

Other events in more than 1% of patients but equally or more frequent in the placebo group included pain, tremor, neuralgia, back pain, dyspepsia, dyspnea, and flu syndrome.

There were no clinically important differences between men and women in the types and incidence of adverse events. Because there were few patients whose race was reported as other than white, there are insufficient data to support a statement regarding the distribution of adverse events by race.

Epilepsy

The most commonly observed adverse events associated with the use of Neurontin® in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of Neurontin® in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see WARNINGS, Neuropsychiatric Adverse Events).

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received Neurontin® in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Incidence in Controlled Clinical Trials

Table 3 lists treatment-emergent signs and symptoms that occurred in at least 1% of Neurontin®-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the Neurontin® group. In these studies, either Neurontin® or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when Neurontin® was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to

estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Table 3. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 Years of Age (Events in at Least 1% of Neurontin® Patients and Numerically More Frequent Than in the Placebo Group)
(Page 1 of 2)

Body System/ Adverse Event	Neurontin®[a] N = 543 %	Placebo[a] N = 378 %
Body As A Whole		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
Cardiovascular		
Vasodilatation	1.1	0.3
Digestive System		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
Hematologic and Lymphatic Systems		
Leukopenia	1.1	0.5
Musculoskeletal System		
Myalgia	2.0	1.9
Fracture	1.1	0.8
Nervous System		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3

[a] Plus background antiepileptic drug therapy

Table 3. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 Years of Age (Events in at Least 1% of Neurontin® Patients and Numerically More Frequent Than in the Placebo Group) (Page 2 of 2)

Body System/ Adverse Event	Neurontin®[a] N = 543 %	Placebo[a] N = 378 %
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
Skin and Appendages		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
Urogenital System		
Impotence	1.5	1.1
Special Senses		
Diplopia	5.9	1.9
Amblyopia[b]	4.2	1.1
Laboratory Deviations		
WBC Decreased	1.1	0.5

[a] Plus background antiepileptic drug therapy
[b] Amblyopia was often described as blurred vision

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of Neurontin®-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with Neurontin®. The incidence of adverse events increased slightly with increasing age in patients treated with either Neurontin® or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Table 4 lists treatment-emergent signs and symptoms that occurred in at least 2% of Neurontin®-treated patients age 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the Neurontin® group. Adverse events were usually mild to moderate in intensity.

Table 4. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial (Events in at Least 2% of Neurontin® Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Neurontin®[a] N = 119 %	Placebo[a] N = 128 %
Body As A Whole		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8
Fatigue	3.4	1.6
Digestive System		
Nausea and/or Vomiting	8.4	7.0
Nervous System		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional Lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
Respiratory System		
Bronchitis	3.4	0.8
Respiratory Infection	2.5	0.8

[a] Plus background antiepileptic drug therapy

Other events in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

Other Adverse Events Observed During All Clinical Trials

Clinical Trials in Adults and Adolescents With Epilepsy

Neurontin® has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials in epilepsy, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to Neurontin® who experienced an event of the type cited on at least one occasion while receiving Neurontin®. All reported events are included

except those already listed in Table 3, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As A Whole: *Frequent:* asthenia, malaise, face edema; *Infrequent:* allergy, generalized edema, weight decrease, chill; *Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent:* hypertension; *Infrequent:* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent:* anorexia, flatulence, gingivitis; *Infrequent:* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare:* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare:* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent:* purpura most often described as bruises resulting from physical trauma; *Infrequent:* anemia, thrombocytopenia, lymphadenopathy; *Rare:* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent:* arthralgia; *Infrequent:* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare:* costochondritis, osteoporosis, bursitis, contracture.

Nervous System: *Frequent:* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent:* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization,

euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare:* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent:* pneumonia; *Infrequent:* epistaxis, dyspnea, apnea; *Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent:* abnormal vision; *Infrequent:* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare:* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Clinical Trials in Pediatric Patients With Epilepsy

Adverse events occurring during epilepsy clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are:

Body as a Whole: dehydration, infectious mononucleosis

Digestive System: hepatitis

Hemic and Lymphatic System: coagulation defect

Nervous System: aura disappeared, occipital neuralgia

Psychobiologic Function: sleepwalking

Respiratory System: pseudocroup, hoarseness

Clinical Trials in Adults With Neuropathic Pain of Various Etiologies

Safety information was obtained in 1173 patients during double-blind and open-label clinical trials including neuropathic pain conditions for which efficacy has not been demonstrated. Adverse events reported by investigators were grouped into standardized categories using modified COSTART IV terminology. Listed below are all reported events except those already listed in Table 2 and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Infrequent:* chest pain, cellulitis, malaise, neck pain, face edema, allergic reaction, abscess, chills, chills and fever, mucous membrane disorder; *Rare:* body odor, cyst, fever, hernia, abnormal BUN value, lump in neck, pelvic pain, sepsis, viral infection

Cardiovascular System: *Infrequent:* hypertension, syncope, palpitation, migraine, hypotension, peripheral vascular disorder, cardiovascular disorder, cerebrovascular accident, congestive heart failure, myocardial infarction, vasodilatation; *Rare:* angina pectoris, heart failure, increased capillary fragility, phlebitis, thrombophlebitis, varicose vein

Digestive System: *Infrequent:* gastroenteritis, increased appetite, gastrointestinal disorder, oral moniliasis, gastritis, tongue disorder, thirst, tooth disorder, abnormal stools, anorexia, liver function tests abnormal, periodontal abscess; *Rare:* cholecystitis, cholelithiasis, duodenal ulcer, fecal incontinence, gamma glutamyl transpeptidase increased, gingivitis, intestinal obstruction, intestinal ulcer, melena, mouth ulceration, rectal disorder, rectal hemorrhage, stomatitis

Endocrine System: *Infrequent:* diabetes mellitus

Hemic and Lymphatic System: *Infrequent:* ecchymosis, anemia; *Rare:* lymphadenopathy, lymphoma-like reaction, prothrombin decreased

Metabolic and Nutritional: *Infrequent:* edema, gout, hypoglycemia, weight loss; *Rare:* alkaline phosphatase increased, diabetic ketoacidosis, lactic dehydrogenase increased

Musculoskeletal: *Infrequent:* arthritis, arthralgia, myalgia, arthrosis, leg cramps, myasthenia; *Rare:* shin bone pain, joint disorder, tendon disorder

Nervous System: *Frequent:* confusion, depression; *Infrequent:* vertigo, nervousness, paresthesia, insomnia, neuropathy, libido decreased, anxiety, depersonalization, reflexes decreased, speech disorder, abnormal dreams, dysarthria, emotional lability, nystagmus, stupor, circumoral paresthesia, euphoria, hyperesthesia, hypokinesia; *Rare:* agitation, hypertonia, libido increased, movement disorder, myoclonus, vestibular disorder

Respiratory System: *Infrequent:* cough increased, bronchitis, rhinitis, sinusitis, pneumonia, asthma, lung disorder, epistaxis; *Rare:* hemoptysis, voice alteration

Skin and Appendages: *Infrequent:* pruritus, skin ulcer, dry skin, herpes zoster, skin disorder, fungal dermatitis, furunculosis, herpes simplex, psoriasis, sweating, urticaria, vesiculobullous rash; *Rare:* acne, hair disorder, maculopapular rash, nail disorder, skin carcinoma, skin discoloration, skin hypertrophy

Special Senses: *Infrequent:* abnormal vision, ear pain, eye disorder, taste perversion, deafness; *Rare:* conjunctival hyperemia, diabetic retinopathy, eye pain, fundi with microhemorrhage, retinal vein thrombosis, taste loss

Urogenital System: *Infrequent:* urinary tract infection, dysuria, impotence, urinary incontinence, vaginal moniliasis, breast pain, menstrual disorder, polyuria, urinary retention; *Rare:* cystitis, ejaculation abnormal, swollen penis, gynecomastia, nocturia, pyelonephritis, swollen scrotum, urinary frequency, urinary urgency, urine abnormality

Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of Neurontin®, the following adverse experiences have been reported in patients receiving marketed Neurontin®. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, Stevens-Johnson syndrome.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of Neurontin® has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of Neurontin® up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Neurontin® is given orally with or without food.

Postherpetic Neuralgia

In adults with postherpetic neuralgia, Neurontin® therapy may be initiated as a single 300-mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID). The dose can subsequently be titrated up as needed for pain relief to a daily dose of 1800 mg (divided TID). In clinical studies, efficacy was demonstrated over a range of doses from 1800 mg/day to 3600 mg/day with comparable effects across the dose range. Additional benefit of using doses greater than 1800 mg/day was not demonstrated.

Epilepsy

Neurontin® is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established.

Patients >12 years of age: The effective dose of Neurontin® is 900 to 1800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules, or 600 or 800 mg tablets. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 or 400 mg

capsules, or 600 or 800 mg tablets three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the TID schedule should not exceed 12 hours.

Pediatric Patients Age 3-12 years: The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of Neurontin® in patients 5 years of age and older is 25–35 mg/kg/day and given in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day). (See CLINICAL PHARMACOLOGY, Pediatrics.) Neurontin® may be administered as the oral solution, capsule, or tablet, or using combinations of these formulations. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize Neurontin® therapy. Further, because there are no significant pharmacokinetic interactions among Neurontin® and other commonly used antiepileptic drugs, the addition of Neurontin® does not alter the plasma levels of these drugs appreciably.

If Neurontin® is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage in Renal Impairment

Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

$$\text{for females } C_{Cr} = (0.85)(140\text{-age})(\text{weight})/[(72)(S_{Cr})]$$
$$\text{for males } C_{Cr} = (140\text{-age})(\text{weight})/[(72)(S_{Cr})]$$

where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL.

Dosage adjustment in patients ≥12 years of age with compromised renal function or undergoing hemodialysis is recommended as follows (see dosing recommendations above for effective doses in each indication).

Table 5. Neurontin® Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
≥60	900-3600	300 TID	400 TID	600 TID	800 TID	1200 TID
>30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
>15-29	200-700	200 QD	300 QD	400 QD	500 QD	700 QD
15[a]	100-300	100 QD	125 QD	150 QD	200 QD	300 QD
		Post-Hemodialysis Supplemental Dose (mg)[b]				
Hemodialysis		125[b]	150[b]	200[b]	250[b]	350[b]

[a] For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

[b] Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

The use of Neurontin® in patients <12 years of age with compromised renal function has not been studied.

Dosage in Elderly

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

HOW SUPPLIED

Neurontin® (gabapentin) capsules, tablets and oral solution are supplied as follows:

100-mg capsules:

White hard gelatin capsules printed with "PD" on one side and "Neurontin®/100 mg" on the other; available in:
Bottles of 100: N 0071-0803-24
Unit dose 50's: N 0071-0803-40

300-mg capsules:

Yellow hard gelatin capsules printed with "PD" on one side and "Neurontin®/300 mg" on the other; available in:
Bottles of 100: N 0071-0805-24
Unit dose 50's: N 0071-0805-40

400-mg capsules:

Orange hard gelatin capsules printed with "PD" on one side and "Neurontin®/400 mg" on the other; available in:
Bottles of 100: N 0071-0806-24
Unit dose 50's: N 0071-0806-40

600-mg tablets:

White elliptical film-coated tablets printed in black ink with "Neurontin® 600" on one side; available in:
Bottles of 100: N 0071-0416-24
Bottles of 500: N 0071-0416-30
Unit dose 50's: N 0071-0416-40

800-mg tablets:

White elliptical film-coated tablets printed in orange with "Neurontin® 800" on one side; available in:
Bottles of 100: N 0071-0426-24
Bottles of 500: N 0071-0426-30
Unit dose 50's: N 0071-0426-40

250 mg/5 mL oral solution:

Clear colorless to slightly yellow solution; each 5 mL of oral solution contains 250 mg of gabapentin; available in:
Bottles containing 470 mL: N 0071-2012-23

Storage (Capsules)
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Storage (Tablets)
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Storage (Oral Solution)
Store refrigerated, 2°-8°C (36°-46°F)

Rx only

Revised May 2002

Capsules and Tablets:

Manufactured by:
Parke Davis Pharmaceuticals, Ltd.
Vega Baja, PR 00694

Oral Solution:

Manufactured for:
Parke Davis Pharmaceuticals, Ltd.
Vega Baja, PR 00694

Distributed by:
Parke-Davis
Division of Pfizer Inc
New York, NY 10017

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/s/

Cynthia McCormick
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